

**UNITED STATES DISTRICT COURT  
SOUTHERN DISTRICT OF NEW YORK**

In re:	)	
OXYCONTIN ANTITRUST LITIGATION	)	04-MD-1603 (SHS)
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PURDUE PHARMA L.P.,	)	This document relates to:
THE P.F. LABORATORIES, INC. and	)	
PURDUE PHARMACEUTICALS L.P.,	)	
	)	
	)	
Plaintiffs and Counterclaim Defendants,	)	
v.	)	
	)	
KV PHARMACEUTICAL COMPANY and	)	07-CIV-3972 (SHS)
ACTAVIS TOTOWA LLC,	)	
	)	
Defendants and Counterclaim Plaintiffs,	)	
v.	)	
	)	
THE PURDUE FREDERICK COMPANY,	)	
THE PURDUE PHARMA COMPANY, and	)	
EUROCELTIQUE S.A.,	)	
	)	
Counterclaim Defendants.	)	
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PURDUE PHARMA L.P.,	)	
THE P.F. LABORATORIES, INC., and	)	
PURDUE PHARMACEUTICALS L.P.,	)	
	)	
Plaintiffs and Counterclaim Defendants,	)	
v.	)	
	)	
KV PHARMACEUTICAL COMPANY,	)	07-CIV-3973 (SHS)
	)	
Defendant and Counterclaim Plaintiff,	)	
v.	)	07-CIV-4810 (SHS)
	)	
THE PURDUE FREDERICK COMPANY,	)	
THE PURDUE PHARMA COMPANY, and	)	
EUROCELTIQUE S.A.,	)	
	)	
Counterclaim Defendants.	)	

**KV PHARMACEUTICAL'S OPENING BRIEF IN SUPPORT  
OF ITS CONTENTION THAT PURDUE'S U.S. PATENT NOS.  
5,549,912, 5,508,042 AND 5,656,295 ARE UNENFORCEABLE  
BECAUSE OF PURDUE'S INEQUITABLE CONDUCT**

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## I. INTRODUCTION

Defendant and Counterclaim-Plaintiff KV Pharmaceutical Company (“KV”) submits this brief on the issue of the inequitable conduct of Plaintiffs and Counterclaim-Defendants Purdue Pharma, L.P. et al. (“Purdue”) in the procurement of U.S. Patent Nos. 5,549,912, 5,508,042 and 5,656,295. More specifically, this brief addresses the issues of Purdue’s intent to deceive the PTO and the balancing of materiality and intent to deceive - the issues remanded to this Court by the United States Court of Appeals for the Federal Circuit in Purdue Pharma L.P. v. Endo Pharmaceuticals Inc., 438 F.3d 1123 (Fed. Cir. 2006) (“Endo”).<sup>1</sup>

The totality of the evidence in the Endo record compels a finding of inequitable conduct. First, Purdue’s wrongful conduct, taken together and in context, is highly material -- without that conduct the patents would not have issued. Second, additional evidence establishes that Purdue undertook its conduct specifically to deceive the PTO, knowing that its statements were not accurate. Weighing materiality and intent to deceive, no doubt exists that Purdue committed inequitable conduct that renders the patents unenforceable.

The Endo record contains strong evidence that Purdue’s failure to disclose material information to the Patent and Trademark Office (“PTO”) was indeed intentional.<sup>2</sup> As previously found both by this Court and by the Federal Circuit, Purdue repeatedly relied during prosecution of the patents-in-suit on the alleged “surprising discovery” that the claimed controlled release (“CR”) oxycodone formulation controls pain over a four-fold dosage range in

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<sup>1</sup> Prior to the settlement of the Endo case, Endo and Purdue filed their respective briefs on remand (Endo D.I. 145, 148, 149). While the Court’s analysis may benefit from the arguments presented in Endo’s briefs, KV does not repeat them here. Also, earlier this year, prior to the settlements of the related Boehringer and Impax cases, Boehringer, Impax and Purdue filed their respective briefs on the remanded inequitable conduct issue. KV relies on and incorporates herein by reference the Endo briefs and the Boehringer and Impax briefs (M.D.L. D.I. 103, 112, 127, 129, and 131) and the facts detailed therein and respectfully requests the Court to consider those briefs in reaching its decision.

<sup>2</sup> Pursuant to the Court’s directive, the evidence relied on here is limited to the trial record of the Endo matter, and all citations to “PTX”, “DX”, or “Tr.”, etc., are to the Endo record.

about 90% of patients, in allegedly sharp contrast to the prior art's eight-fold dosage range. Purdue repeatedly described this distinction in terms of "Surprisingly Improved Results", "clinical significance", and "Results Obtained", communicating to the PTO that the alleged distinction between OxyContin<sup>®</sup> and other opioid analgesics was a discovery made after clinical tests and based on empirical evidence. This communication succeeded: the purported narrower dosage range was the sole basis upon which the rejections were overcome. Purdue's statements were affirmative misrepresentations that misled the Examiner on the state of the experimental record which was at the crux of the Examiner's inquiry.

As the Federal Circuit found, Purdue clearly implied that it had actual clinical data to support the alleged "discovery", while it in fact had no such support, withholding the fact that the "discovery" was actually based only on theoretical "insight". The Federal Circuit affirmed that this concealment constituted a withholding of material information, albeit not highly material.

The Federal Circuit was not aware, however, that Purdue did not merely lack actual evidence to back up its "discovery". Much more than that, while the patents were pending, Purdue actually conducted -- and concealed -- clinical studies comparing the effective dosage ranges of CR oxycodone and the prior art CR morphine. *The results of those non-disclosed studies did not support, and in fact directly contradicted, the alleged "discovery" repeatedly relied on during prosecution.* Purdue's withheld clinical studies showed that CR oxycodone and CR morphine were actually only *comparable* in terms of dosage range. Thus, not only did Purdue, as the Federal Circuit recognized, lack experimental support for its "surprising discovery" assertion, the alleged discovery -- which was pointedly relied upon by Purdue to overcome the Examiner's obviousness rejection -- was actually contradicted by

Purdue's own concealed clinical studies. Purdue never disclosed these clinical results to the Patent Examiner, nor did Purdue ever retract its "surprising discovery" assertions. Under these circumstances, a finding that Purdue's misrepresentations and omissions were both highly material and intended to deceive the PTO is clearly warranted, and a balancing of materiality and intent clearly supports a renewed holding of inequitable conduct.

In addition to the misrepresentations and omissions above, Purdue also submitted a misleading declaration of Dr. Robert Kaiko to the PTO that suggested he was an independent expert but concealed his substantial connection with the inventors. There is also strong evidence that CR oxycodone's discovery was not a "surprise" at all as Dr. Kaiko repeatedly told the PTO, but was in fact expected, in view of the invention's similarities to the prior art and the fact that Purdue's development of CR oxycodone was the *fifth* opioid formulation it had developed with the "surprising" profile alleged here.

There is thus ample clear and convincing evidence for this Court to conclude that Purdue's misrepresentations and omissions were intentional and deceitful, as well as highly material.<sup>3</sup> A balancing of the evidence of materiality and intent overwhelmingly supports a renewed holding of inequitable conduct and unenforceability of Purdue's patents.

## **II. BACKGROUND**

KV Pharmaceutical Company, a Delaware corporation having its principal place of business in St. Louis, Missouri, is a specialty pharmaceutical company and a leader in

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<sup>3</sup> Purdue has engaged in a long-term pattern of deceit in order to protect its multi-billion dollar pain control franchise. In addition to its dealings with the PTO, this pattern can also be seen in its and its executives' May 2007 guilty pleas to criminal charges that its marketing campaign for OxyContin® misled regulators, doctors and patients about CR oxycodone's properties and drug abuse potential. The fines amounted to over \$600 million. Those charges were based on activities dating back to 1995, the same period that the patents-in-suit were pending. Purdue's misrepresentations to the PTO and to the public were part and parcel of Purdue's overall scheme to ensure that CR oxycodone would maintain its highly lucrative monopoly by deceptive means.

developing innovative products using its advanced drug delivery technologies. KV develops and markets both branded and generic pharmaceutical products.

In 2006 and 2007, KV submitted Abbreviated New Drug Applications (“ANDAs”) to the FDA under §505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355(j)) for 10, 15, 20, 30, 40, 60, and 80 mg strength CR oxycodone HCl tablets. KV’s ANDAs include “Paragraph IV” certifications stating that Purdue’s U.S. Patent Nos. 5,549,912 (“‘912 patent”), 5,508,042 (“‘042 patent”) and 5,656,295 (“‘295 patent”) are invalid, unenforceable or will not be infringed by KV’s manufacture, use or sale of its CR oxycodone products.

Purdue sued KV for patent infringement on January 16, 2007 and again on February 12, 2007 in the Delaware District Court within 45 days of receiving KV’s Paragraph IV notices for its 10, 20, 40 and 80 mg dosages and its 30 and 60 mg dosages, respectively. On June 6, 2007, Purdue sued KV for infringement of the same patents in this Court based on KV’s ANDA filing for its 15 mg dosage of CR oxycodone. On May 16, 2007, the Judicial Panel on Multidistrict Litigation, on Purdue’s motion, transferred the Delaware cases against KV to this Court so as to become a part of the In re Oxycontin Antitrust Litigation, 04-MD-1603 (SHS). Final FDA approval of KV’s ANDA is stayed pending a final judgment on the infringement claims or the passing of 30 months, whichever occurs first.

### **III. LEGAL STANDARD**

“Inequitable conduct occurs when a patentee breaches his or her duty to the PTO of ‘candor, good faith, and honesty.’” Ferring B. V. v. Barr Labs., Inc., 437 F.3d 1181, 1186 (Fed. Cir. 2006) (citations omitted). “One who has engaged in inequitable conduct has inflicted damage on the patent examining system, obtaining a statutory period of exclusivity by improper means, and on the public, which must face an unlawfully-granted patent. Loss of one’s patent



and damage to reputation are justified penalties for such conduct.” Molins PLC v. Textron, Inc., 48 F.3d 1172, 1182 (Fed. Cir. 1995). Inequitable conduct includes “affirmative misrepresentations of material facts” and “also arises when the patentee fails to disclose material information to the PTO.” Ferring, 437 F.3d at 1186.

“The inequitable conduct analysis is performed in two steps . . . .” Id. The first step requires “a determination of whether the withheld reference meets a threshold level of materiality and intent to mislead.” Id. The second step requires “weighing . . . the materiality and intent in light of all the circumstances to determine whether the applicant’s conduct is so culpable that the patent should be held unenforceable.” Id. A higher intent showing can outweigh a “proportionately” lower materiality finding. Endo, 438 F.3d at 1135; see also Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc., 326 F.3d 1226, 1234 (Fed. Cir. 2003) (required level of materiality or intent may rise or fall in proportion to the level of the other element).

The Federal Circuit’s decision in Endo confirms that it is up to this Court, as the finder of fact, to assess the credibility of the witnesses. By remanding the issue to this Court, the Federal Circuit necessarily vested this Court with discretion to make factual findings on Purdue’s intent and to balance the materiality of Purdue’s misrepresentations and omissions with its intent to deceive the PTO. This Court can and should exercise its ultimate discretion in deciding to hold the patents unenforceable because of Purdue’s inequitable conduct.

#### **IV. ARGUMENT**

There is extensive evidence in the Endo record demonstrating that Purdue had the motivation and intent to deceive the PTO by engaging in a protracted pattern of intentionally misrepresenting and omitting material information in its dealings with the PTO.

**A. The Federal Circuit Affirmed This Court’s Finding That Purdue Materially Misled The PTO**

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To overcome the PTO’s obviousness rejections of the application for U.S. Patent No. 5,266,331 (“‘331 patent”), parent of the patents-in-suit, the applicants claimed that they discovered that their CR oxycodone formulation “acceptably control[led] pain over a four-fold range of dosages in approximately 90% of patients.” See Endo, 438 F.3d at 1130. Purdue also argued that the “clinical significance” of the reduced dosage range of oxycodone was a more efficient titration process than “other opioid analgesics requiring approximately twice the dosing range.” (DX 2008 at EN205620, EN205641).

Purdue repeated these statements in the applications that matured into the patents in suit. Thus, “[d]uring prosecution of the ‘912 patent, Purdue again found it necessary to distinguish its controlled release oxycodone formulations over prior art . . . by emphasizing its ‘surprising discovery’ of oxycodone’s four-fold dosage range and more efficient titration process.” See Endo, 438 F.3d at 1131.

During prosecution, Purdue repeatedly used language implying that there was clinical support for its claims. Purdue quantified its “unexpected results” in numerically precise terms, referring to specific dosage ranges for specific percentages of patients, and discussed those “results” in the context of clinical studies. Ironically, Dr. Kaiko’s Declaration and Attachment argued that in vivo results could not be predicted from in vitro properties, and stressed the need for actual clinical results as a predicate for any conclusions about the in vivo properties of a drug. Dr. Kaiko’s declaration asserted that “[e]xtensive clinical studies are required before regulatory approval of even a close derivative of a well-known drug.” (DX 2008 at EN205636) (emphasis added). Dr. Kaiko further emphasized the importance of “well-controlled therapeutic evaluations” in obtaining “the most meaningful therapeutic conclusions

and extrapolations.” (*Id.*, ¶16). The Kaiko Attachment referred to “[t]he *clinical significance provided* by [OxyContin®] at dosage range of *10 to 40 mg q12h* for acceptable pain management in approximately *90%* of patients.” (DX 2008 at EN205641) (emphasis added).

Purdue, however, had no test results or scientific evidence to support the asserted dosage range. The Federal Circuit noted that the presence of clinical studies “was clearly to be inferred from the language used by Purdue in both the patents and prosecution history.” *Endo*, 438 F.3d at 1131. As a result, the Federal Circuit concluded that “Purdue’s arguments to the PTO provide enough of a suggestion that clinical trials had been performed that failure to tell the PTO [that] the discovery was based on Dr. Kaiko’s insight and not scientific proof was a *failure to disclose material information*.” *Id.* (emphasis added).

**B. Purdue Intended To Deceive The PTO And Had A Strong Motivation To Extend Its CR Opiate Revenue Stream**

“Direct evidence of intent to deceive or mislead the PTO is rarely available but may be inferred from clear and convincing evidence of the surrounding circumstances.” *See Endo*, 438 F.3d at 1133-34 (internal citations omitted). Here, Purdue’s intent to mislead need not be inferred simply from its many misrepresentations and omissions. Instead, extensive evidence demonstrates that Purdue acted deliberately and with a specific deceptive intent over many years.

As an initial matter, Purdue’s misconduct implicates both the applicants and the prosecuting patent attorney, and took place over the course of multiple applications and over multiple years, which is indicative of deceptive intent. “[M]ultiple omissions over a long period of time . . . heightens the seriousness” of a single omission. *Ferring*, 437 F.3d at 1194 (citing *Refac Int’l, Ltd. v. Lotus Dev. Corp.*, 81 F.3d 1576, 1582 (Fed. Cir. 1996)). This conclusion flows from the common sense proposition that a repeated failure to disclose material information is less likely to have an innocent explanation. For example, in *Li Second Family L.P. v. Toshiba*

Corp., 231 F.3d 1373 (Fed. Cir. 2000), the court inferred deceptive intent from the applicant's failure to disclose a material PTO Board of Appeals decision while making "numerous statements during prosecution" that were contrary to the withheld decision. Id. at 1381. The Federal Circuit affirmed the conclusion that the applicant's "persistent course of nondisclosure and misrepresentation constituted inequitable conduct." Id. See also Golden Valley Microwave Foods, Inc. v. Weaver Popcorn Co., Inc., 837 F. Supp. 1444, 1471 (N.D. Ind. 1992), aff'd mem., 11 F.3d 1072 (Fed. Cir. 1993) ("[t]he facts include too many instances of the withholding of material information for any conclusion to be reached other than that the withholding and mischaracterizations were done with the intent to mislead the Patent Office"); Merck & Co., Inc. v. Danbury Pharmacal, Inc., 873 F.2d 1418, 1421-22 (Fed. Cir. 1989) (patentee's pattern of misrepresentations showed deceptive intent).

Moreover, a finding that the patentee had a strong motive to mislead the PTO supports a finding that the patentee acted with culpable intent. Digital Control Inc. v. The Charles Mach. Works, 437 F.3d 1309, 1320 (Fed. Cir. 2006). Here, Purdue had an unusually strong motive to mislead: Purdue's flagship product for moderate to severe pain was at risk, and Purdue faced the prospect of losing a vital revenue stream to generic competition if its CR oxycodone patents did not issue. Purdue developed CR oxycodone intending that it would replace CR morphine (MS Contin<sup>®</sup>) in the market. Dr. Kaiko was actively searching for a "hook" or a "selling point" to persuade doctors and patients to switch from CR morphine because it "may be lost to generic competition." (DX 3156).

Purdue could not rely on its earlier Oshlack U.S. Patent No. 4,861,598 ("598 patent") to keep CR oxycodone safe from generic competition. The '598 patent covered only the AcroContin (CR oxycodone) formulation, not its effects in the body. (DX 2048). Generic

competitors could (and indeed did) devise a formulation that achieved OxyContin's results without infringing the '598 patent. Mr. Oshlack himself had devised multiple controlled-release formulae for oxycodone and cited to them in the specification of the patents in suit. In short, Purdue and Dr. Kaiko needed the '331 patent and the patents-in-suit to issue, or Purdue risked losing a very large revenue stream. Indeed, CR oxycodone accounted for almost \$5 billion in sales from 1996 through 2002. (PTX 877A).

In Digital Control, the Federal Circuit agreed with the district court's view that "overwhelming evidence" that an inventor was under "pressure from his largest customer . . . to acquire and enforce patent rights" was a significant factor in finding that the inventor acted with intent to deceive. See Digital Control, 437 F.3d at 1320. Here, the Purdue personnel faced intense internal pressure to ensure that CR oxycodone would not be lost to generic competition.

Given this motivation to extend its vital CR opiate revenue stream, it has become apparent that Purdue's pattern of misleading the PTO was part of a broad strategy to promote OxyContin® at all costs, and was not limited to mere inequitable conduct. In addition to making material misrepresentations and omissions and withholding critical contradictory test results from the PTO, infra, Purdue, through its executives and employees, engaged in a criminal marketing campaign to ensure OxyContin®'s success by deceptive means. Beginning in 1995, while all of the applications for the patents-in-suit were pending, and continuing to 2001, Purdue misled FDA regulators, doctors and the public about OxyContin®'s addictive profile and potential for drug abuse. With intent to mislead and deceive, Purdue marketed OxyContin® as less addictive, less subject to abuse and less likely to cause withdrawal than other opioids. Those representations, like those made to the PTO, were false. As a result, Purdue and three named

executives were charged with and pleaded guilty to criminal violations of misbranding under the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§301, et seq.<sup>4</sup>

**C. Purdue's Misrepresentations And Omissions Were Both Highly Material And Clearly Intentional**

**1. Purdue's Deceptive Intent Can Be Inferred From The Fact That CR Oxycodone Was An Expected, Not A Surprising, Development**

It is undisputed that Purdue had no clinical data or other scientific evidence supporting its representations to the PTO that CR oxycodone provided for a reduced dosage range and improved titratability. The Federal Circuit affirmed this Court's findings that Purdue's withholding from the PTO of its knowledge that the alleged reduced dosage range and improved titratability benefit were mere theories and not proven facts constituted a withholding of material information from the PTO.

Purdue characterized CR oxycodone's alleged reduced dosage range and ease of titration relative to CR morphine as a "surprise." But nothing about this theory was a "surprise": Purdue expected CR oxycodone to have a reduced dosage range and more effective titration relative to morphine based entirely on the well-known properties of the drug. In a July 16, 1990 memorandum, Dr. Kaiko explained that oxycodone's known "characteristics" would lead to a "more efficient titration process" and a more stable "stabilization process." (DX 3165 at P664252-53). On September 28, 1993, Dr. Kaiko reiterated that "[o]ne would expect that [oxycodone's] characteristics would translate into a number of desirable clinical outcomes such

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<sup>4</sup> In May 2007, Purdue pleaded guilty to the criminal charges in the United States District Court for the Western District of Virginia. In its Plea Agreement, Purdue admitted guilt to felony charges of misbranding a drug with intent to defraud or mislead. Purdue agreed to pay over \$600 million in penalties to various federal and state agencies for its misconduct. The three executives each pleaded guilty to the misdemeanor offense of misbranding a drug and agreed to pay a total of \$34 million for their offenses. Specifically, Michael Freedman, Purdue's President and Chief Executive Officer, admitted guilt and paid \$19 million in fines. Howard R. Udell, Purdue's Vice President and General Counsel, admitted guilt and paid \$8 million in fines. Paul D. Goldenheim, Purdue's Vice President and Medical Director who testified in the Endo patent case, admitted guilt and paid \$7.5 million. See Barry Meier, Narcotic Maker Guilty of Deceit Over Marketing - Producer of Oxycontin to Pay \$600 Million, N.Y. Times, May 11, 2007, at A1.

as . . . the finding that a narrower range of dosages of oxycodone are required to manage a group of patients than with the utilization of drugs with a lower oral bioavailability.” (DX 3629 at P037082-83).

*Significantly, Purdue had previously developed CR versions of four other opiates: morphine, codeine, dihydrocodeine and hydromorphone, all of which had the same dissolution profile as CR oxycodone.* All of these CR formulations had a 2-4 hour  $T_{\max}$  (time of maximum blood concentration) and a 12-hour pain relief profile. Yet Purdue persisted in telling the PTO that CR oxycodone’s properties were “surprising”, even though CR oxycodone was Purdue’s fifth successful development of a CR opioid with this profile.

Purdue failed to disclose that based on its known properties and on the repeated prior development of similar CR opioid drugs, Purdue *expected* CR oxycodone to have a reduced dosage range and be easier to titrate. Purdue’s misleading claim that it was “surprised” by the known properties of the drug is further compelling evidence of its intent to deceive the PTO with repeated material misrepresentations and/or omissions.

## **2. Purdue Falsely Claimed That A 2-4 Hour $T_{\max}$ With 12 Hours Of Pain Relief Was “Surprising”**

Purdue claimed that achieving 12 hours of pain relief with a  $T_{\max}$  of 2-4 hours for OxyContin® was “surprising.” (DX 2008 at EN205583-584, 585). Through its attorney, Mr. Steinberg, Purdue asserted that “*it is totally impossible to predict what dissolution rates for any particular drug will give rise to an extended duration of action, e.g. a 12-hour duration of action as set forth in this case.*” (DX 2008 at EN205630 (emphasis added)). Those assertions were false, and contradicted by extensive testimony from Purdue’s own witnesses at trial. In reality, Purdue was not “surprised” by the  $T_{\max}$  of 2-4 hours or 12 hours of pain relief because:

- Purdue’s objective was to mimic CR morphine’s *in vivo* effects, including a  $T_{\max}$  of 2-4 hours and 12 hours pain relief (Tr. 504, 570-71, 578);

- Purdue had already achieved these *in vivo* effects successfully with four other opioid analgesic drugs (morphine, dihydrocodeine, codeine, and hydromorphone) (see Impax Br. (D.I. 112) at 3-6);
- Purdue had a reasonable expectation that the targeted *in vitro* dissolution profile would yield the desired *in vivo* results (Tr. 571; see Impax Br. (D.I. 112) at 7-8); and
- Once Purdue matched CR codeine's *in vitro* profile, CR oxycodone yielded the desired *in vivo* results on the first try (Tr. 289-91).

In short, nothing in Purdue's documents suggests that Purdue expected to fail. Rather, Purdue expected CR oxycodone to work for its intended purpose, just like the prior opiates.

Purdue did not claim "surprise" by mere happenstance. Purdue chose the word "surprise" to counter any suggestion that it had 'a reasonable expectation of success' that its oxycodone formulation would achieve a 2-4 hour  $T_{\max}$  and 12 hours of pain relief. See, e.g., Alza Corp. v. Mylan Labs., Inc., 464 F.3d 1286, 1293-94 (Fed. Cir. 2006); Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1162 (Fed. Cir. 2006). "One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of "unexpected results," *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward -- that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." In re Soni, 54 F.3d 746, 750 (Fed. Cir. 1995). Indeed, Purdue made these assertions in response to the PTO's request to submit a declaration to demonstrate such "unexpected results" in order to overcome a finding of obviousness.

Purdue has not provided any reasonable explanation as to why it claimed that the 2-4 hour  $T_{\max}$  and 12 hours pain relief were a "surprise." Mr. Steinberg's assertion that "it is totally impossible to predict what dissolution rates for any particular drug will give rise to an extended duration of action" is contradicted by internal Purdue documents showing that Purdue copied MS Contin<sup>®</sup>'s *in vitro* dissolution profile in order to achieve the same *in vivo* results, by



testimony that Purdue had a reasonable expectation of success, and by the fact that Purdue obtained the desired *in vivo* results on the first try.

Purdue's U.S. Patent No. 4,834,984 (CR dihydrocodeine), Purdue's CR codeine formulation, and Purdue's CR hydromorphone formulation all have a  $T_{\max}$  of between 2-4 hours and 12 hours pain relief. (DX 2047, col. 2, ln. 18-21; DX 2826 ( $T_{\max}$  shown in Abstract 27), Tr. 479-80, 1229, DX 2706 ( $T_{\max}$  3.3 hrs); DX 2045, col. 2, ln. 19-26). But Purdue did not disclose the '984 patent or the codeine formulation to the PTO. Had the Examiner known that Purdue had in fact achieved the same results with four prior drugs, the Examiner would have been less likely to credit Purdue's claim of "surprise" and he would likely have required test data or clinical evidence in support of the alleged "surprise" or unexpected results.

Mr. Steinberg testified that he did not disclose the dihydrocodeine patent because he believed that patent was "cumulative" of the hydromorphone patent, which had been disclosed. (Tr. 1613, 1632-33, 1607). Dr. Kaiko testified that it did not need to be disclosed because dihydrocodeine was not indicated for "moderate to severe pain". (Tr. 456). Neither explanation holds water.

The '984 patent itself contradicts the first excuse: the very first sentence of the patent recites that dihydrocodeine is used to treat moderate to severe pain. (DX 2047, col. 1, ln. 5-7). See Merck, 873 F.2d at 1419 (affirming materiality of undisclosed tests showing that another drug "shar[ed] a pharmacological resemblance" with the patented formulation and "behave[d] similarly in a variety of tests"). Dr. Kaiko similarly testified that Purdue's CR codeine formulation did not need to be disclosed because codeine was not prescribed for "moderate to severe pain," but Purdue's own documents reflect that CR codeine was a direct

competitor to CR oxycodone for “moderate to moderately severe cancer pain.” (Tr. 456; DX 3184 at P775189).

The second excuse, that the ‘984 patent was cumulative, fares no better. That which is surprising once becomes a lot less surprising when it has been achieved five times. See Critikon Inc. v. Becton Dickinson Vascular Access, 120 F.3d 1253, 1257 (Fed. Cir. 1997) (rejecting a patentee’s “conclusory” cumulateness claim when considering intent to deceive); Monsanto Co. v. Rohm & Haas Co., 456 F.2d 592, 599-600 (3<sup>rd</sup> Cir. 1972) (claiming surprise imposes obligation to disclose what claim of surprise is relative to). In Novo Nordisk Pharm., Inc. v. Bio-Technology Gen. Corp., 424 F.3d 1347, 1362 (Fed. Cir. 2005), the Federal Circuit rejected a similar cumulateness argument, holding that multiple “failed attempts to practice an invention are relevant evidence of non-enablement.” By analogy, multiple successful attempts to achieve a particular result are evidence of lack of surprise, and thus relevant evidence of obviousness.

The materiality of these prior withheld formulations with a 2-4 hour  $T_{\max}$  and 12 hours of pain relief is high. Purdue argued that the claims should issue because “[a]pplicants’ discovery herein that oxycodone in a matrix having the dissolution *in vivo* and the other characteristics set forth in the claims of this case would provide 12 hours of relief when administered orally, clearly constitutes a patentable invention.” (DX 2008, EN205630, ‘331 file history, Paper 7, Mar. 10, 1993, p. 2). Had the PTO known that Purdue had achieved this “surprising result” on at least four prior occasions, the PTO would likely have questioned the novelty and non-obviousness of these results.

This evidence of Purdue’s intent to deceive is strong: both Dr. Kaiko and Mr. Steinberg made a deliberate decision to withhold material prior art. Purdue has no credible

explanation for failing to disclose its own prior art with a 2-4 hour  $T_{\max}$  and 12 hours of pain relief while simultaneously professing to have been surprised to have achieved those same results. The balancing of Purdue's non-disclosure with its intent to deceive compels a finding that the patents in suit are unenforceable.

**3. Purdue Intentionally Misrepresented Dr. Kaiko To Be An Independent Expert, Omitting The Fact That He Was Affiliated With Euroceltique's Parent And The Original Applicants**

In the original patent application for the '331 parent patent, the PTO Examiner requested a declaration to support what Mr. Steinberg had said during his interview with the Examiner: "Applicant will submit proposed declaration supporting unobviousness and unexpected results." (DX 2008, EN205626, '331 file history, Paper 6, Feb. 25, 1993). In response, Mr. Steinberg submitted a declaration from Dr. Kaiko, identifying him only as a Purdue employee, omitting that Purdue was the parent company of the assignee EuroCeltique and that Dr. Kaiko worked with the inventors. (*Id.* at EN205630, Paper 7, Mar. 10, 1993). The Examiner had no way of knowing that Dr. Kaiko was not an independent, disinterested party, but rather had an intimate connection to the alleged invention, the applicants (his co-workers), and the assignee, EuroCeltique.

The Federal Circuit has affirmed findings of unenforceability based on similar omissions. "We have previously held that a declarant's prior relationships with the patent applicant may be material, and that failure to disclose such relationships to the Examiner may constitute inequitable conduct." *Ferring*, 437 F.3d at 1187-88. In *Refac*, the Examiner rejected an affidavit from a co-inventor as "self-serving," so the applicant submitted affidavits from three individuals without disclosing that *one* of the three individuals had worked for the inventors' company for a short eight-week period and was already familiar with the invention. *Refac*, 81 F.3d at 1581-82. The Federal Circuit affirmed a finding of inequitable conduct that rendered the

patent unenforceable. Id. at 1585; see Ferring, 437 F.3d at 1194-95 (patent unenforceable because patentee did not disclose declarants' affiliation with the assignee); Paragon Podiatry Lab., Inc. v. KLM Labs., Inc., 984 F.2d 1182, 1190-92 (Fed. Cir. 1993) (same).

Significantly, the affidavits in Refac and Ferring did not involve any affirmative misrepresentation. Purdue's failure to disclose Dr. Kaiko's affiliation with EuroCeltique and the inventors goes further than the omissions found sufficient to render the patent unenforceable in Refac. Dr. Kaiko knew about and had worked on the invention claimed in the '331 patent, just like the declarant in Refac. But Dr. Kaiko was also a senior executive with Purdue, and thus had a significant stake in the patent's success, unlike the declarant in Refac, who had no ongoing relationship with the patentee. Here, as in Refac, "[t]he inference of an intent to mislead arises not simply from the materiality of the affidavits, but from the affirmative acts of submitting them, their misleading character, and the inability of the examiner to investigate the facts." Refac, 81 F.3d at 1582 (quoting Paragon, 984 F.2d at 1191).

The Court has already found a material omission in the failure to disclose the lack of clinical data supporting the assertions about reduced dosage range and ease of titration, and the Federal Circuit has affirmed this finding. The record shows, however, that Purdue's behavior went well beyond this, revealing a pattern of deception, half-truths and a motive to mislead. See Refac, 81 F.3d at 1582 (inequitable conduct evaluation may take into account conduct that does not itself "constitute[] inequitable conduct [but] heightened the effect" of the misleading omission). The Federal Circuit has sustained unenforceability findings where "prophetic" examples were presented as fact, Novo Nordisk, 424 F.3d 1347, where the patentee failed to disclose that a portion of a video was shot with a different lens, Frazier v. Roessel Cine Photo Tech. Inc., 417 F.3d 1230 (Fed. Cir. 2005), and where an example was described in the past

tense where there was no experimental evidence to support that claim, Hoffman-La Roche, Inc. v. Promega Corp., 323 F.3d 1354 (Fed. Cir. 2003). The conduct here, taken as a whole, is at least as serious.

**4. Purdue's Attempt To Distance Itself From The Kaiko Declaration Is Futile**

Purdue's recent claim that the Attachment to the Kaiko declaration submitted to the PTO to overcome the examiner's rejection of the claims of the parent '331 patent application (DX 2008, EN205638ff) was submitted as "nothing more than a clerical error" simply highlights Purdue's and Dr. Kaiko's lack of credibility. (Purdue 6/12/06 Br. on Endo Remand at 12). The fact is that Purdue repeatedly relied on the Kaiko Declaration and Attachment during the prosecution history, at trial, and in pleadings to this Court. Purdue and Dr. Kaiko cannot now disavow it. In an analogous situation, a district court entered summary judgment that a statement made to the PTO was materially misleading, and in subsequent proceedings the inventor "attempted to blame the problem on his attorney." Digital Control, 437 F.3d at 1320. The district court found, and the Federal Circuit agreed, that this claim was "unworthy of credence" because it came after the district court's decision that the representation was materially misleading. Id. Here, too, Dr. Kaiko's new "explanation" for the Kaiko Attachment comes only after a determination by this Court—affirmed by the Federal Circuit—that the Attachment contained a materially misleading omission. As in Digital Control, Dr. Kaiko's belated explanation deserves no credence.

**5. Purdue's Material Representations To The Patent Examiner Were Contradicted By Purdue's Own Internal Documents**

As the Federal Circuit recognized, the applicants' and their attorneys' representations regarding the reduction in daily dosage ranges (resulting in the comparative ease of titratability) were made in such a way as to imply that clinical data existed to support the

“surprising discovery”, even though, as Purdue admitted, it did not. Endo, 438 F.3d at 1133. However, it is evident that these representations actually were false, and that at least one of the applicants (Dr. Kaiko) had knowledge of the falsity of these representations during the pendency of the patents in suit.

Purdue’s repeated statements during prosecution and in the specifications of the ‘331, ‘912, ‘042, and ‘295 patents that CR oxycodone unexpectedly controls pain over a four-fold range in approximately 90% of patients, while other opioids, in particular CR morphine and hydromorphone, require an eight-fold range, allowing for more efficient titration using CR oxycodone, were not supported by actual data. In fact, those representations were contradicted by Purdue’s own studies.

An internal Purdue memorandum authored by Dr. Kaiko as well as Dr. Kaiko’s trial testimony confirm that despite Purdue’s representations to the PTO that these unexpected results and consequential benefits had been demonstrated, there existed no clinical support for the representations, and Dr. Kaiko knew it. In the internal memorandum, dated September 28, 1993, almost one full year after the filing of the application for the ‘912 patent, Dr. Kaiko wrote:

One would expect that [oxycodone’s] characteristics would translate into a number of desirable clinical outcomes such as: . . . the finding that a narrower range of dosages of oxycodone are required to manage a group of patients than with the utilization of drugs with a lower oral bioavailability. (DX 3629 at P037082-83).

Dr. Kaiko requested that the memorandum recipients focus on such an outcome and also that they examine each of their ongoing and planned studies as potential candidates for supporting a “claim” that the primary advantage of OxyContin<sup>®</sup> over MS Contin<sup>®</sup> (CR morphine) and other strong opioids is that OxyContin<sup>®</sup> is “the most efficiently titratable strong analgesic.” (Id. at P037083).

Dr. Kaiko admitted that Purdue had been unable to demonstrate whether CR oxycodone provides a more efficient titration than, for example, CR morphine:

You should know that the “claim” is theoretically rational but practicably and inherently difficult to demonstrate, in part, because of the extraordinary degree of “noise” typically associated with analgesic studies and, in part, because of the fact that none of our ongoing and planned studies have been specifically designed to address such issues. We should not be discouraged or even surprised in finding “no apparent differences” between the use of OxyContin and other therapies in respect to the “claim.” It, in fact, may only be with the development of such special studies that the “claim” can be effectively supported. (*Id.*).

At trial, Dr. Kaiko conceded that at the time the patent applications were filed, he had “no scientific proof” for the representations made in the specifications of the ‘912, ‘042 and ‘295 patents regarding reduction in range of daily dosages, but only an insight. Purdue Pharma L.P. v. Endo Pharmaceuticals Inc., 70 U.S.P.Q.2d 1185, 2004 U.S. Dist. LEXIS 10, at \*70 (S.D.N.Y. Jan. 5, 2005); Tr. 407.

Purdue repeatedly misled the PTO by implying that the reduction in range of daily dosages (and the consequential increased efficiency of titratability) had been proven, when, in reality, this alleged unexpected result of applicants’ invention was merely theoretical. Purdue’s false and/or misleading representations that it had been found that the oxycodone formulations of the invention permitted a narrower dosage range vis-a-vis morphine and other opioids were repeated over and over to surmount the prior art, despite the fact that Dr. Kaiko – a named inventor of the ‘912, ‘042 and ‘295 patents -- knew full well that these results had not actually been obtained. This in itself illustrates Purdue’s intent to deceive.

The seriousness of these misrepresentations and the intent of Dr. Kaiko and Purdue to deceive the PTO, however, is underscored by the fact that when relevant studies were actually conducted, the results of these studies, never disclosed to the PTO, showed that the

alleged invention did not result in a narrower dosage range in comparison to CR morphine or hydromorphone.

**6. There Is Clear And Convincing Evidence That Purdue Intended To Deceive The Patent Examiner**

The ‘912, ‘042 and ‘295 applicants’ and solicitor’s material omission that the “surprising discovery” was not based on actual evidence, but rather on insight, was not made inadvertently or in good faith. As shown by the documents summarized above, Purdue (and specifically at least Dr. Kaiko) knew, while the “surprising discovery” was still being urged as a reason the patents should be allowed, that there was information -- known only to Purdue -- that was contrary to the “surprising discovery” allegation. If Purdue believed that this information -- and the withheld clinical studies, infra -- could be somehow “explained away”, then it should have presented it to the Examiner and it should have proceeded to attempt to do so. Yet at no time during the pendency of the ‘912, ‘042 or ‘295 patent applications was the PTO informed of this highly material information, which would have undermined Purdue’s reliance on the alleged unexpected results even more than had the Examiner been told that the “discovery” was just an insight.

The withheld information, especially when added to the material omission that the “discovery” was based only on insight, would have been highly material to prosecution of the ‘912, ‘042 and ‘295 patent applications, and puts Purdue’s behavior in a different light, creating a strong inference that Purdue intended to deceive the PTO.

A great deal of the evidence that Purdue and its named inventor Kaiko intended to deceive the Patent Examiner has already been noted by this Court, including that:

(a) Dr. Kaiko testified during the Endo trial that, as this Court summarized, “at no time prior, during, or subsequent to the prosecution of the patents in suit did there exist at



Purdue a ‘set of procedures and methods’ that could ‘provide definitive conclusions’ that OxyContin<sup>®</sup> was ‘the most easily titratable strong analgesic,’ and that such a test would require ‘hundreds of thousands of patients.’” Purdue, 2004 U.S. Dist. LEXIS 10, at \*79 (citing Tr. 235, 246).

(b) Purdue researcher Dr. Goldenheim testified at the Endo trial that, as this Court summarized, “as of October 20, 1993, Purdue’s researchers ‘weren’t anywhere close’ to proving that OxyContin<sup>®</sup> was ‘the most efficiently titratable long-acting strong analgesic . . .’” Id. (citing Tr. 984).

(c) As stated in the specifications of the patents-in-suit, a reduction in dosage ranges would directly impact titration. (See, e.g., the ‘295 and ‘912 patents, col. 4, ll. 51-63 and the ‘042 patent, col. 4, ll. 53-65). Accordingly, this Court recognized that “Purdue’s admitted inability to prove titration claims undercuts any good faith belief that the inventions provided pain relief for most patients over a reduced, four-fold dosage range.” Purdue, 2004 U.S. Dist. LEXIS 10, at \*81.

(d) A July 16, 1990 internal memorandum written by Dr. Kaiko, referring to the alleged narrower dosage range and improved ease of titration, concedes that:

While the theoretical argument may be relatively strong using available data, it may be difficult to demonstrate these claims within the context of efficacy studies. Thus, an acceptance of a priority program for controlled-release oxycodone should not assume that all these claims can be demonstrated. See id. at \*81 (citing DX 3165).

(e) Just four months before filing the ‘331 patent application, Dr. Goldenheim wrote to Dr. Kaiko and others at Purdue that “OxyContin may have advantages over MS Contin in terms of less variability in dose required.” See id. at \*81-82 (quoting DX 3226) (emphasis added by Court). In the memo dated September 28, 1993, almost a year after Purdue represented

to the PTO that it had “surprisingly discovered” the inventions’ reduced dosage range, Dr. Kaiko wrote that “one would expect that [oxycodone’s] characteristics would translate into a number of desirable clinical outcomes such as: . . . the finding that a narrower range of dosages of oxycodone are required to manage a group of patients than with the utilization of drugs with a lower oral bioavailability.” See id. at \*82 (quoting DX 3629). Thus, long after representing to the PTO that a narrower range of dosages and ease of titration were “surprising discoveries,” internal memoranda reveal that Dr. Kaiko considered his “surprising discovery” to be a mere “expectation” in need of scientific support. See id. The controversial nature of Dr. Kaiko’s expectation was confirmed later by Dr. Goldenheim, who, in response to Dr. Kaiko’s assertion that OxyContin® was the “most efficiently titratable long-acting strong analgesic,” wrote “this is a theory – not yet proven. We will have to see.” See id. at \*82-83 (citing DX 3156).

(f) As this Court noted, “Purdue attempts to limit many of these comments as only being made in the context of Purdue’s efforts to receive FDA approval for the comparative claim ‘most efficiently titratable strong analgesic,’ and accordingly [argues that] these comments do not address any assertions Purdue made to the PTO about the reduced dosage ranges of the patents in suit.” Id. at \*83 (quoting Tr. 982) . The Court added, “[h]owever, . . . a reduced dosage range is directly related to easier titration; any concerns about proving the latter must affect belief in the former, especially as Purdue’s reduced dosage range assertion is – like the titration assertion - made in a comparative context - i.e., ‘other opioid analgesics require approximately twice the dosage range.’” Id. (citing the ‘295 and ‘912 patents, 4:51-63 and the ‘042 patent, 4:53-65).

(g) As this Court concluded: “Accordingly, . . . any good faith belief that Purdue had ‘discovered’ the reduction in dosage range is substantially undercut by its admitted

inability to prove, or even to develop, a ‘set of procedures and methods’ to prove this reduction in dosage range (and related ease of titration), and cannot ‘overcome an inference of intent to mislead.’” Id. at \*83-84.

In combination with the above evidence summarized by this Court, the withheld contradictory clinical studies discussed infra provide clear and convincing evidence of intent to deceive. Purdue, Dr. Kaiko, and the applicants failed to disclose to the PTO during the prosecution of any of the patents-in-suit that their representation that the invention surprisingly provided the benefit of a four-fold dosage range which could adequately treat 90% of patients for pain and thus was superior to the prior art MS Contin<sup>®</sup> product was directly contradicted by clinical studies designed and carried out by Purdue with the knowledge of Dr. Kaiko and, in some cases, under the direct supervision of Dr. Kaiko.

Accordingly, the representations that the invention provides for a four-fold dosage range and improved titratability over the prior art MS Contin<sup>®</sup> product constituted intentional and knowing affirmative misrepresentations made to deceive the PTO and gain allowance over the MS Contin<sup>®</sup> prior art which Purdue, Dr. Kaiko and the inventors knew to be comparable in dosage range and titratability to the invention claimed.

**7. Purdue Withheld Highly Material Clinical Studies From The PTO Which Contradicted Its Representations Of Dosage Range And Titratability, Thus Further Revealing Its Deceptive Intent**

It is beyond dispute that Purdue’s repeated representations to the PTO that its CR oxycodone invention reduced the dosage range necessary to treat patients and thereby improved titratability was not merely material, but highly material, to the examiner’s allowance of the Purdue patent claims.

When the parent '331 application was under rejection as unpatentable in view of the prior art Goldie '341 patent directed to CR hydromorphone, Purdue argued for allowance over this reference by representing to the patent examiner that:

The expertise and time of physicians and nurses, as well as the duration of unacceptable pain patients must endure during the opioid analgesic titration process is substantially reduced through the efficiency of the controlled release oxycodone formulations of the present invention. (DX 2008, EN205620, '331 file history, Paper 4, Oct. 22, 1992, p. 4).

\* \* \*

It is respectfully submitted that one skilled in the art having knowledge of the controlled release oxycodone [sic, hydromorphone] formulations of Goldie, et al. would not be motivated to prepare controlled release oxycodone formulations in a dosage range from about 10 mg to about 40 mg, which formulations thereby acceptably control pain over a substantially narrower, approximately four-fold range in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients utilizing controlled release hydromorphone, or controlled release opioid analgesics in general. (DX 2008, EN205621, '331 file history, Paper 4, Oct. 22, 1992, p. 5) (emphasis original).

The materiality of the reduced dosage range and improved titratability representations by Purdue is confirmed by the examiner's statement of reasons for allowance in the prosecution of the '042 patent, as follows:

None of the references of record singly anticipate or in combination motivate one with ordinary skill in the art to formulate the particular method for reducing the dosage of oxycodone as set forth in the claims. (DX 2009, EN205735, '042 file history, Paper 6, Dec. 24, 1995, p. 2).

It is also undisputed that Purdue had no clinical data or other scientific evidence supporting its representations to the PTO that the invention did, in fact, provide for a reduced dosage range and improved titratability. The Federal Circuit has affirmed this Court's findings that Purdue's withholding from the PTO of its knowledge that the alleged reduced dosage range

and improved titratability benefit were mere theories and not proven facts constituted a withholding of material information from the PTO.

However, this is not the only material information that Purdue withheld from the PTO. Purdue, contemporaneously, while continuing to represent to the PTO over a five-year period that CR oxycodone controlled pain using only a four-fold dosage range in sharp contrast to the eight-fold dosage range required for the prior art CR morphine, carried out clinical studies which directly contradicted its representations to the PTO (see, e.g., PTX 475; PTX 717). Yet Purdue chose not to disclose any of this clinical work to the PTO. Purdue's withheld clinical information was highly material since it would have revealed to the Patent Examiner that Purdue's representations of a reduced dosage range and improved titratability over the CR morphine prior art were, in fact, knowing false representations. As a result, Purdue's withholding of contradictory clinical information is clear and convincing evidence of Purdue's intent to deceive the Patent Examiner in repeatedly relying and continuing to rely on the argument that it had first propounded to the PTO during the prosecution of the '331 patent:

It has now been surprisingly discovered that the presently claimed controlled release oxycodone formulations acceptably control pain over a substantially narrower, approximately four-fold [range] (10 to 40 mg every 12 hours - around-the-clock dosing) in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients for opioid analgesics in general (emphasis in original). (DX 2008, EN205619, '331 file history, Paper 4, Oct. 22, 1992, p. 3) (emphasis original).

\* \* \*

The expertise and time of physicians and nurses, as well as the duration of unacceptable pain patients must endure during the opioid analgesic titration process is substantially reduced through the efficiency of the controlled release oxycodone formulations of the present invention. (DX 2008, EN205620, '331 file history, Paper 4, Oct. 22, 1992, p. 4).

During the period February 22, 1994 through May 16, 1995, prior to the issuance of any of the patents-in-suit,<sup>5</sup> Purdue conducted a clinical study (the Kalso study, No. OC93-0303) comparing the invention - CR oxycodone - to the prior art CR morphine. Dr. Kaiko was aware of the Kalso study from its inception in early 1994. (Tr. 423-24). On October 17, 1996, Purdue issued a report setting forth the clinical results (PTX 475). This report was specifically reviewed and approved by Dr. Kaiko, whose signature appears on page P275624 of the report. The report concluded that there were “no significant differences” during titration to stable pain control between the invention and the controlled release prior art.

The median number of days to stable pain control during titration was not significantly different between treatments: 3.0 days with CR oxycodone and 1.5 days with CR morphine. Despite the fact that morphine was the more common prior analgesic, there were no significant differences in time to stable dosing for patients titrated with oxycodone or morphine. (PTX 475 at P275647 (p. 26), final paragraph).

This conclusion by Purdue and by Dr. Kaiko totally contradicts the representation that the invention - CR oxycodone - improves titratability as well as Purdue’s representation to the PTO that it had surprisingly discovered this alleged superiority of CR oxycodone. Purdue’s own clinical work shows that the CR oxycodone did not improve titratability as compared to the prior art CR morphine and, in fact, that it was the CR morphine that was slightly superior with respect to titratability, i.e., the data showed that the number of days to stable pain control using CR morphine was only 1.5 days as compared to 3 days with CR oxycodone.<sup>6</sup> The conclusions of this report are reproduced below in pertinent part:

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<sup>5</sup> The ‘192, ‘042 and ‘295 patents issued on August 27, 1996, April 16, 1996, and August 12, 1997, respectively.

<sup>6</sup> Similarly, on May 3, 1994, the Purdue OxyContin Project Team received a memo regarding the “OxyContin Tablet Investigator Survey Preliminary Report.” The investigators’ survey obtained responses from “investigators treating cancer patients” regarding OxyContin®’s clinical effects. As the cover memo explained, “the investigators’ comments are important” because “they are actually using the drug.” The survey results showed that none of the physicians responding to the survey found OxyContin® easier to titrate than MS Contin®: “0/11 felt it was easier [to titrate] than MS Contin.” (DX 3739). Purdue did not submit the Oxycontin Survey to the PTO.

**5. CONCLUSIONS:** Results of this study demonstrate that CR oxycodone effectively controls pain in cancer patients. Overall, the Q-statistic indicates that CR oxycodone and CR morphine had comparable efficacy. Although there were some statistically significant differences between treatments in pain intensity scores, these differences were small and not clinically meaningful. There were no significant differences in pain intensity scores between treatments on phlebotomy days. CR oxycodone was judged to provide cancer patients with effective pain control that was clinically equivalent to that provided by CR morphine.

The median number of days to stable pain control during titration was not significantly different between treatments: 3.0 days with CR oxycodone and 1.5 days with CR morphine. Despite the fact that morphine was the more common prior analgesic, there were no significant differences in time to stable dosing for patients titrated with oxycodone or morphine.

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In addition to contradicting Purdue's titratability claims, the same clinical study (No. OC93-0303) also showed that the dosage ranges for both the alleged invention, CR oxycodone, and the prior art, CR morphine, were quite comparable and at least six-fold for each -- not four-fold for the invention and eight-fold for the prior art as Purdue repeatedly represented to the PTO. One of the tables summarizing the results of the study shows that the "Final Total Daily Dose" after completion of titration (the lower set of numbers in the table) for the patients who took CR oxycodone ranged from 40 mg to over 200 mg, and for those who took CR morphine ranged from 60 mg to over 300 mg, both six-fold ranges. (If the "max" dosages listed are taken into account (480 mg for CR oxycodone and 840 mg for CR morphine) then the ranges are twelve-fold and fourteen-fold respectively - still hardly the four-fold/eight-fold range comparison of the Kaiko "insight".) (See PTX 475 at Table 5A, P275725):

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PROTOCOL NO. OC93-0303  
TABLE 5A  
SUMMARY OF OPEN LABEL TITRATION  
Population: All Patients Enrolled in Study

	CR Oxycodone		CR Morphine		Total	
	N	%	N	%	N	%
Entered Titration	23	(100.0)	22	(100.0)	45	(100.0)
No. Entered Double-Blind	17	( 73.9)	19	( 86.4)	36	( 80.0)
Initial Total Daily Dose @ (CR Oxycodone / CR Morphine)						
40 / 60	8	( 34.8)	8	( 36.4)	16	( 35.6)
80 / 120	7	( 30.4)	4	( 18.2)	11	( 24.4)
120 / 180	4	( 17.4)	4	( 18.2)	8	( 17.8)
160 / 240	1	( 4.3)	1	( 4.5)	2	( 4.4)
200 / 300	1	( 4.3)	2	( 9.1)	3	( 6.7)
> 200 / > 300	2	( 8.7)	3	( 13.6)	5	( 11.1)
N	23		22			
Mean	100.9 *		182.7 *			
Std. Error	15.9		33.1			
Min	40		60			
Max	320		660			
Final Total Daily Dose @ (CR Oxycodone / CR Morphine)						
40 / 60	4	( 17.4)	5	( 22.7)	9	( 20.0)
80 / 120	5	( 21.7)	6	( 27.3)	11	( 24.4)
120 / 180	4	( 17.4)	3	( 13.6)	7	( 15.6)
160 / 240	1	( 4.3)	3	( 13.6)	4	( 8.9)
200 / 300	3	( 13.0)	0	( 0.0)	3	( 6.7)
> 200 / > 300	6	( 26.1)	5	( 22.7)	11	( 24.4)
N	23		22			
Mean	167.0		231.8			
Std. Error	25.6 #		46.4 #			
Min	40		60			
Max	480		840			

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(Continued)

CROSS REFERENCES:

Data Listing: 1, 9.2A, 9.2B, 12.1A, 12.1B and 12.1C  
Statistics: Appendix IV

\* Statistically significant difference between variances ( $p=0.0015$ ) and means (adjusted for unequal variances:  $p=0.0335$ ).

# Statistically significant difference between variances ( $p=0.0101$ ).

@ No statistically significant differences in distribution of doses.



In a second Purdue study (the Berman/Mucci-LoRusso study, No. OC92-1001) (see PTX 717), conducted during the period June 1, 1994 through December 27, 1995, Purdue obtained similar results.<sup>7</sup> The report on this study was issued on September 27, 1996 and concluded that:

CR oxycodone was *as effective as* CR morphine in relieving pain in cancer patients. The median time to achieve stable pain control was two days with both treatments, and the number of dose adjustments required and rescue medication use were similar for both drugs. (PTX 717 at P187373; P187423 (emphasis added)).

The report further concluded that “this study provides definitive evidence of the *clinical equivalence* of CR oxycodone and CR morphine in controlling cancer pain.” (Id. at P187374; P187423 (emphasis added)).

In the OC92-1001 study, Purdue determined that CR morphine produced stable pain release with a five-fold dosage range (60-300 mg) while the allegedly superior CR oxycodone invention required an even wider nine-fold dosage range (40-360 mg). The five-fold dosage range for CR morphine and nine-fold dosage range for the alleged CR oxycodone invention, which were also noted in a published article based on this study,<sup>8</sup> appear in the study report as reproduced below (PTX 717 at P187448):

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<sup>7</sup> Like the Kalso study, the Berman/Mucci-LoRusso study was concluded prior to the issuance of any of the patents-in-suit. In fact, both studies were concluded before the application that led to the ‘295 patent was filed on March 19, 1996. Dr. Kaiko was involved with and aware of the Berman study during the pendency of the patents-in-suit, and testified that at the time he reviewed the final report he was aware that the ‘295 application was pending. (Tr. 421-22).

<sup>8</sup> DX 2844 at EN000280, Mucci-LoRusso et al., 2 Euro. J. Pain 239, 243 (1998). The article, which was co-authored by Dr. Kaiko, also stated that “[d]ose titration was similar with the two treatments. . . . CR oxycodone was as easily titrated to the individual’s need for pain control as CR morphine.” (Id. at 243, 248 (EN000280, 285)).

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PROTOCOL NO. OC92-1001  
TABLE 5.2A  
SUMMARY OF FINAL DAILY DOSE TO ATTAIN STABLE PAIN  
Population: Patients Valid for Pharmacokinetic/Pharmacodynamic Analysis

	CR Oxycodone		CR Morphine		Total	
	N	%	N	%	N	%
Daily Dose (CR Oxycodone / CR Morphine)						
40 / 60	16	(41.0)	10	(25.0)	26	(32.9)
80 / 120	7	(17.9)	16	(40.0)	23	(29.1)
120 / 180	7	(17.9)	7	(17.5)	14	(17.7)
160 / 240	6	(15.4)	5	(12.5)	11	(13.9)
200 / 300	1	(2.6)	2	(5.0)	3	(3.8)
360 / 540	2	(5.1)	0	(0.0)	2	(2.5)
N	39		40		79	
Mean	100.5		139.5		120.9	
Std. Error	12.5		10.8		8.9	
Min	40		60		50	
Median	80		120		100	
Max	360		300		450	

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CROSS REFERENCES:  
Data Listing: 5.2

Even if the four highest final dosages (top 10%) for the 39 patients who took CR oxycodone, and the four highest final dosages (top 10%) for the 40 patients who took CR morphine, are removed from the calculation, in the OC92-1001 study both CR oxycodone and CR morphine required four-fold dosage ranges to attain stable pain control for about 90% of the patients (40-160 mg and 60-240 mg, respectively). *Id.* At best, therefore, this study showed that CR oxycodone and CR morphine were only *comparable* in terms of the narrowness of the dosage range and the time to achieve a stable dose.

This is confirmed by the testimony of Purdue Medical Director Dr. Paul Goldenheim:

Q. So in terms of the time to achieve the stable dose, CR OxyCodone was comparable to CR – controlled release morphine, correct?

A. That's what this study appears to have found, yes.

(Goldenheim 08/03/01 Dep. Tr. 252:15-19 (deposition from Boehringer case made part of Endo trial record)).

In clinical study after clinical study, Purdue found and reported that the dosage ranges needed to relieve pain for the alleged invention - CR oxycodone - and the prior art CR

morphine - were comparable. These studies did not find or report that the alleged invention had any superiority over the prior art with respect to an improved dosage range or improved titratability. Yet, incredibly, Purdue repeatedly continued to represent to the PTO that it had discovered that its CR oxycodone invention did permit a reduced four-fold dosage range in sharp contrast to the eight-fold range required for the CR morphine prior art and that the invention, therefore, was clinically significant since it improved titratability.

Purdue has argued that these clinical studies are not relevant because they related to attempts to obtain FDA approval for comparative labeling claims regarding the ease of titration. See also Endo, 438 F.3d at 1134 (noting quantum of proof for FDA approval is higher than that required by the PTO, and criticizing this Court's finding that any good faith on Purdue's part was undercut by its admitted inability to prove the titration claim). But Purdue's reports on the clinical studies outlined above had nothing to do with any FDA marketing claim, although they were ultimately submitted to the FDA. Instead, as Purdue conceded at page 22 of its opening appeal brief to the Federal Circuit, study OC92-1001 was designed to

examine "titration of OxyContin versus MS Contin" without regard to what marketing claim Purdue would ultimately seek in the FDA (quoting DX 3632 at P057354).

Moreover, as noted above, the Purdue studies not only failed to prove greater ease of titration for CR oxycodone as compared to CR morphine, as focused on by the Federal Circuit, they also contained data showing that the relative dosage ranges were not four-fold to eight-fold, but were rather only comparable at best. This was completely at odds with Purdue's "surprising discovery" representations to the PTO, regardless of the purpose for which the studies were conducted.

The clear inconsistency between the representations that Purdue and Dr. Kaiko made in the clinical studies presented to the FDA and the representations they made to the PTO

to gain allowance of the asserted patents is powerful evidence of intent to deceive. Merck, 873 F.2d at 1422 (submission of data to FDA that was withheld from PTO was “damning” evidence of intent to mislead the PTO).

Dr. Kaiko’s intent to mislead the PTO was further highlighted by his testimony at the Endo trial regarding the OC92-1001 study report, which he approved and which was sent to the FDA but not the PTO. When confronted with the conclusions of the report, which stated that CR oxycodone and CR morphine were comparable, Dr. Kaiko attempted to disavow the conclusions:

- Q. Could you turn to the conclusions paragraph on page 75 of the study report, page [P]187423.
- A. Yes.
- Q. This indicates a date of September 27, 1996.
- A. Yes.
- Q. Were you aware at the time that at least one of your patent applications, the ‘295 patent application, was pending?
- A. Yes.
- Q. And I direct your attention to the third paragraph of the conclusions. And I read it to you and ask whether this is your recollection, your correct understanding that at the time as a conclusion, final conclusion of the Mucci-LoRusso study, quote, CR oxycodone was as effective as CR morphine in relieving pain in cancer patients. The median time to achieve stable pain control was two days with both treatments, and the number of dose adjustments required in rescue medication used were similar for both drugs. Do you recall that you were aware of that at the time, in roughly September of 1996?
- A. Yes, but I had indicated yesterday the study wasn’t designed to determine whether there was a difference or not.
- Q. It wasn’t designed as a titration study?
- A. It wasn’t designed to determine whether there was a difference or not in terms of titration, that is correct.

Q. So that conclusion shouldn't be there. It shouldn't be included in the conclusions portion?

A. This study did not either prove or disprove time to stable pain control.

Q. Do you think it would have been information important for the patent examiner to know in assessing whether you had in fact surprisingly found a reduction in dosage range?

A. No.

(Tr. 421-23). Dr. Kaiko's testimony that the information was not "important" and his attempt to say that the report did not reach certain conclusions even though those conclusions were expressly set forth in the report and designated as "Conclusions," is simply not credible. Dr. Kaiko's stonewalling and evasiveness confirms and further reveals a clear intent to deceive not only the PTO, but this Court.

When Purdue's representations of the *superiority* of the invention repeatedly made to the PTO to overcome the examiner's rejections of unpatentability over the prior art are viewed together with Purdue's and Dr. Kaiko's conclusions of mere *comparability* of the invention to the prior art based upon clinical tests, it is apparent that Purdue's withholding of information from the PTO was not some technical mistake concerning whether its discovery of the four-fold dosage range and titratability benefit was scientifically proven or simply Dr. Kaiko's theoretical insight. What is apparent, instead, is that Purdue and Dr. Kaiko falsely represented and continued to represent that they had discovered the four-fold dosage range benefit and resulting improved titratability over the prior art when, in fact, they conducted and reported on detailed clinical studies *which showed the opposite*. Purdue and Dr. Kaiko then further deliberately concealed the falsity of their representations to the PTO by withholding from the patent examiner the very clinical data that would have revealed to the PTO that their repeated representations about their discovery of an improved dosage range and associated titratability

benefit were untrue. Absent a confession, there can be no stronger proof of an intent to deceive than exists in this case.

As the Federal Circuit held in Merck & Co., Inc. v. Danbury Pharmacal, Inc., 873 F.2d 1418 (Fed. Cir. 1989), the simultaneous submission of data to the FDA and withholding of that same data from the PTO was evidence “rightly described by the [District Court] as ‘damning.’” Id. at 1422 (affirming finding of intent to mislead the PTO). In Merck, the applicant had withheld from the PTO studies regarding the muscle relaxant properties of a prior art drug (amitriptyline), while submitting such information to the FDA as part of a Investigational New Drug Application. Id. at 1419. Merck’s excuse for not disclosing this information to the PTO even though it was disclosed to the FDA was that the information was merely cumulative and that the FDA required comparisons with amitriptyline. Id. at 1419-20. The Federal Circuit found the withheld information (which showed that “amitriptyline’s activity was comparable to” the activity of the claimed compound) to be material and not merely cumulative because

amitriptyline was, as indicated in Merck’s own tests, by far the most relevant to skeletal muscle relaxation. To FDA, Merck disclosed amitriptyline, not the cited prior art to which it now says amitriptyline would have been merely cumulative.

Id. at 1421. The court concluded that the inconsistency between the test data presented to the FDA and presented to the PTO was strong evidence of intent to deceive:

In light of all the evidence rightly described by the court as “damning”, including . . . the simultaneous submission of amitriptyline data to [the] FDA and its withholding from the PTO, . . . we cannot say that the court’s finding of intent to mislead was clearly erroneous.

Id. at 1422.

Purdue has attempted to distinguish Merck, arguing that in its FDA submissions, Merck stated that its drug caused drowsiness, while it told the PTO the drug was free of side

effects. Purdue argues that here, Purdue's submission to the FDA of data for the purpose of getting permission to market OxyContin® as "easy to titrate" was consistent with its PTO submissions, not inconsistent. (Purdue Br. in opposition to Boehringer Br., at 21). First, however, Purdue ignores Merck's submission of amitriptyline data to the FDA while withholding that data from the PTO, which was a separate act considered by the court in arriving at its finding of inequitable conduct. Second, Purdue did in fact make inconsistent disclosures to the FDA and the PTO just as occurred in Merck. It submitted studies to the FDA containing dosage range data indicating that CR oxycodone and CR morphine had *comparable* dosage ranges, while it continued to represent to the PTO that those dosage ranges were *not comparable*, but rather four-fold and eight-fold, and to imply that it had scientific evidence of this when in fact it had no such evidence at all.

A case involving inconsistent data decided by the Federal Circuit subsequent to its decision in the Endo case is strikingly similar to this case. Cargill, Inc. v. Canbra Foods, Ltd., 476 F.3d 1359 (Fed. Cir. 2007), concerned a patent directed to a non-hydrogenated canola oil formulation called IMC 130 possessing allegedly superior oxidative stability. During prosecution, the patent examiner rejected the claims based on a prior art publication (Wong), disclosing an oil with a similar fatty acid composition to IMC 130, which the examiner believed would have similar properties due to its similar chemical structure. Id. at 1362. The applicant responded that test data in the specification showed that two oils with similar fatty acid compositions, IMC 130 and another oil called IMC 129, had strikingly different oxidative stability properties. Id. at 1362-63. After several further rejections and responses, the claims were allowed, the examiner explaining that this data showed that "one cannot predict the oxidative stability of an oil based on the fatty acid composition of the oil." Id. at 1363.

Despite having overcome the rejection based on the alleged striking superiority of IMC 130 over IMC 129, the applicant did not disclose to the PTO a report containing

test data indicating that three samples of IMC 129 oil exhibited oxidative stabilities of 32, 35 and 32 AOM hours, which is a range similar to and, at one point, overlapping that of IMC 130 [which had an oxidative stability of 35 to 40 AOM hours].

Id. at 1365.

The applicant argued that this contrary data was not material because the tests were “performed under unusual conditions” and were thus not comparable to the data submitted to the examiner. Id. at \*1365-66. The Federal Circuit found this to be no excuse, stating that

“[M]ateriality is determined from the viewpoint of a reasonable patent examiner, and not the subjective beliefs of the patentee”. . . . A reasonable examiner would certainly want to consider test data that is directly related to an important issue of patentability. . . .

Id. at 1366 (citation omitted).

The court further found that the repeated nature of the omission supported the District Court’s finding of intent to deceive:

[T]here were multiple occasions that called for disclosure of the omitted data. . . . The repeated omission . . . is relevant because “intent may be inferred where a patent applicant knew, or should have known, that withheld information would be material to the PTO’s consideration of the patent application.” Critikon, 120 F.3d at 1256. An applicant should know information is material when the examiner repeatedly raises an issue to which the information relates.

Id. at 1366. The court affirmed the holding of inequitable conduct, noting that even if the applicant honestly believed IMC 130 to be patentable, this was no excuse for withholding information the applicant knew or should have known was material. Id. at 1367 (“[c]lose cases should be resolved by disclosure, not unilaterally by the applicant”; applicants should not make or rely “on their own determinations of materiality” (citations omitted)).



Similarly, when Purdue obtained the Kalso and Berman data showing that its claim of superiority of the dosage range of CR oxycodone might be called into question by that data, which was the only data available to Purdue regarding the relative dosage ranges and comparative titratability of CR oxycodone and CR morphine, it should have disclosed that data to the PTO. The fact that Purdue withheld this data, aside from being a highly material omission in its own right, creates a strong inference that Purdue's representations alleging that it had "surprisingly discovered" the unexpected result of a reduced dosage range, despite the fact that it had no actual data to support that claim, were made with an intent to deceive the PTO. The clinical study data bore directly on this issue, and showed the dosage ranges to be merely comparable. This data would have raised grave doubts about whether there was any difference in dosage range or titratability of the two drugs, yet Purdue still persisted in relying on the "surprising discovery" and withheld the contrary data from the PTO, because to do otherwise would have forced Purdue to reveal that its "discovery" of unexpected dosage range results was not in fact supported by any scientific data, but only by Dr. Kaiko's insight. This is strong evidence of intent to deceive.

## **V. CONCLUSION**

Purdue procured the patents in suit by engaging in a pattern of intentional material omissions and misrepresentations that went to the heart of patentability. When the PTO rejected the claims as being merely the expected and obvious results of the prior art CR formulations, Purdue claimed a series of "surprising results" in a desperate attempt to overcome those rejections. Purdue claimed to be "surprised" by *in vivo* properties that it in fact had "reasonably expected" to achieve, while concealing evidence that it had already achieved those same results for similar prior art drugs on a total of four prior occasions. Purdue submitted Dr. Kaiko's Declaration omitting the material fact of his relationship with the original inventors and their

employer. Purdue represented to the PTO that it had made a surprising clinical discovery of the four-fold dosage benefit when in fact it had no clinical support at all, but only Dr. Kaiko's theoretical insight. Finally, Purdue failed to tell the PTO about its clinical results that flatly contradicted Purdue's arguments for patentability. The materiality of Purdue's many repeated misrepresentations and omissions, considered together, is extremely high.

Purdue's many repeated material misrepresentations and omissions, taken together, are clear and convincing evidence of Purdue's intent to deceive the PTO into issuing the patents-in-suit. The pattern of deception was repeated by both the inventor, Dr. Kaiko, and the prosecuting attorney, Mr. Steinberg, in four separate patent prosecutions, one after the other, over a period of years. Purdue's explanations for its misrepresentations and failures to disclose are self-serving and not credible. Purdue had a tremendous business motive to deceive the PTO, and in fact did so. In this case, the balancing of materiality and evidence of intent to deceive must lead to the inevitable conclusion that Purdue's conduct in dealing with the PTO was inequitable. Accordingly, this Court should exercise its discretion to hold the patents in suit unenforceable because of Purdue's inequitable conduct.

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Respectfully Submitted,

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**CERTIFICATE OF SERVICE**

I hereby certify that I caused a true and correct copy of **KV PHARMACEUTICAL'S OPENING BRIEF IN SUPPORT OF ITS CONTENTION THAT PURDUE'S U.S. PATENT NOS. 5,549,912, 5,508,042 AND 5,656,295 ARE UNENFORCEABLE BECAUSE OF PURDUE'S INEQUITABLE CONDUCT** to be served on September 21, 2007 via CM/ECF to all the listed parties.

s/ John F. Sweeney

John F. Sweeney